EXHIBIT B

TVT Expert Report of Marc R. Toglia, M.D.

I. Qualifications

I am a sub-specialist in the field of Female Pelvic Medicine and Reconstructive Pelvic Surgery. I am double board certified in Female Pelvic Medicine and Reconstructive Surgery (2012) and Obstetrics and Gynecology (1995) and am licensed to practice medicine in Pennsylvania. Currently I serve as the Chief of Female Pelvic Medicine and Reconstructive Surgery for the Main Line Health System in suburban Philadelphia. I also hold the academic title of Associate Professor of Obstetrics and Gynecology at Thomas Jefferson School of Medicine and Associate Clinical Professor at the Lankenau Institute of Medical Research (LIMR).

I received my Doctor of Medicine from Vanderbilt University School of Medicine in 1989, and completed an Obstetrics and Gynecology residency at the University of Michigan Medical Center in 1993. During my residency, I trained under renowned urogynecologist Dr. John Delancey and the urologist Edward McGuire, MD, a pioneer in the development of sling surgery for women. During both my undergraduate and graduate career, I was actively involved in both basic science and clinical research at Duke University Medical Center, the Howard Hughes Medical of Molecular Biology at Vanderbilt University and Vanderbilt University Medical Center.

After graduating from residency, I accepted a position as assistant professor of Obstetrics and Gynecology at the State University of New York at Stony Brook, where I helped to establish the division of Urogynecology with Andrew Fantl, MD and Joseph Schaffer, MD, two other notable urogynecologists. In 1996, I moved to Philadelphia, where I established the Division of Urogynecology at the Main Line Health System in suburban Philadelphia. I maintain a busy clinical practice, performing over 200 female reconstructive procedures a year, oversee the residency training in Female Pelvic Medicine at the Lankenau Medical Center, serve as an associate clinical researcher at the Lankenau Institute of Medical research.

I am an internationally recognized expert in the field of Urogynecology. I currently serve as an editor for the two premier urogynecology medical journals -- Female Pelvic Medicine & Reconstructive Surgery (FPMRS) and the International Urogynecology Journal (IUJ), and serve active leadership roles in the American Urogynecologic Society and the Society for Gynecologic Surgeons.

I have over 34 years of experience in clinical and basic science research. I have published numerous scholarly articles within the field of medicine since 1984 on a wide range on subjects. Additionally, I have authored numerous medical textbook chapters and I am a co-author of the textbook Office Urogynecology. I have published scholarly articles concerning gynecology, urogynecology and urinary incontinence in many of our premier medical journals including the New England Journal of Medicine, American Journal of Obstetrics and Gynecology, Obstetrics and Gynecology, IUJ and FPMRS. My clinical research has included authorship of a randomized clinical trial comparing the retropubic TVT with a third generation sling, as well as a retrospective cohort examining complications with native tissue repairs with permanent sutures for vaginal reconstruction. These studies have been presented at both national and international scientific meetings.

Throughout my career, I have performed thousands of gynecologic surgeries, specifically female pelvic floor reconstruction, such as abdominal sacral colpopexy, vaginal approaches including vaginal hysterectomy, high uterosacral suspensions, sacrospinous ligament suspensions, native tissue repair, biologic graft and synthetic mesh augmented repairs. I was trained to perform retropubic colposuspensions by Drs. John Delancey and Andrew Fantl, and autologous fascial pubovaginal slings by Dr. Edward McGuire. I am considered one of the leading experts in the greater Philadelphia region on surgical revision of complications related to vaginal mesh procedures.

I was trained on and have performed the Gynecare TVT procedure since 1999, shortly after it was introduced in the United States. I have performed over 2,500 retropubic TVTs over the past 14 years. I have also performed other mid-urethral sling procedures including the transobturator approach (TVT-O, TVT Abbrevo) and mini slings, such as the TVT Secur. I also perform the TVT Exact, which is analogous to the original TVT, and served as a consultant to Gynecare on its development. I have actively participated in the Ethicon Professional Education for these products and have trained other surgeons, including Urogynecologists, Urologists, and Gynecologists from around the country. I have served as faculty in a wide range of professional educational activities, including invited lectures, cadaver labs, as well as proctoring and preceptorships. I have also consulted on the design and the analysis of other prototype procedures.

For additional information please refer to my attached Curriculum Vitae.

II. Materials Reviewed

In preparation of my opinions I have searched and reviewed the medical and scientific literature concerning the efficacy and safety of TVT and suggesting or contesting that the TVT is defectively designed in that it is not reasonably safe for its intended use in women who are implanted with it. I have also reviewed the Ethicon TVT Instructions for Use, Professional Education materials made available to users of TVT (pelvic floor surgeons), TVT Surgeons Resource Monograph, and other Ethicon documents, Professional society analyses, systematic and other reviews, guidance and statements. A list of these materials and those that I may use at trial are attached to this report. I have also reviewed the Plaintiffs' expert reports and the materials cited by Plaintiffs' experts.

III. Fees and Expert Testimony

My fees for serving as an expert in this matter are: $400/hour for review, report drafting and meetings and $4,000/day for deposition and trial testimony. I have given expert deposition testimony in the prior four years in the Mullins v. Ethicon TVT case on October 2, 2015.

IV. Opinions

What follows are my opinions and the bases for the opinions. They are based on my education, training, professional experience, clinical research and teaching I have performed, my review of the medical and scientific literature, as well as my experience as an editor for the leading medical journals in my field. They are also a reflection of my annual participation in the annual scientific meetings of national and international medical societies since 1993, including the published Position Statements and Systematic Review Guidelines of these societies. All of my opinions are held to a reasonable degree of medical and scientific certainty. In summary, in my opinion, the TVT's design is reasonably safe for its intended use, no other design or mesh has been demonstrated to be more effective, safer, or has been studied as much, as long, or in as many patients and types of patients as the TVT has showing that it is safe and effective, and the TVT IFU, Surgeons Monograph and Professional Education are adequate to warn of the risks of the TVT device as discussed below.

A. The usefulness and desirability of TVT — its utility to surgeons and to the public as a whole.

In order to discuss the utility and usefulness of the TVT's design one must first consider the background of stress urinary incontinence and its treatment. Stress Urinary Incontinence is a highly prevalent condition that affects approximately 1 in 3 adult women at some point in their lives. Approximately 1 in 4 women with urinary incontinence consult a healthcare professional for this condition. It is an often debilitating and bothersome condition that can substantially reduce a woman's quality of life. It is associated with significant physical morbidity, sexual dysfunction and a reduction in psychological well being, as well as a loss of independence and reduction in social interactions. It also has significant cost implications to the individuals and the healthcare system. The estimated annual cost in the USA is over 20 billion dollars (Fantl 1996, Hu 2004).

Surgical treatment of incontinence is considered to be the most clinically and cost effective first line therapy for this condition. Prior to midurethral sling procedures, traditional surgical approaches included the retropubic urethropexy (e.g., Burch colposuspension and the MMK), "bladder neck" slings, which include autologous fascial slings and the "needle-type" urethral suspensions such as the Raz and Stamey procedures. All of these procedures are associated with significant intraoperative risks, including surgical hemorrhage, hematoma formation and injury to adjacent structures. Urinary tract and visceral injuries are well recognized complications of these procedures, and include bladder, ureteral and urethral injury (Stanton 1985). Additionally, the two most popular anti- incontinence procedures of the 1980's-1990's were associated with lengthy operating times, inpatient hospital stays averaging 3 days, and a lengthy recovery period.

Urinary tract injuries have been reported to occur in 6.3% of pubovaginal sling procedures (Summitt et al, 1992). Erosion rates of up to 21% have been reported with traditional bladder neck slings that utilize synthetic materials (Beck 1998; Bent 1993; Bryans 1979; Muznai 1992). It is also a common complication of the Stamey type suspensions (Mundy 1993; Jarvis 1992). Voiding dysfunction, both short and long term, is one of the most common complications of traditional anti-incontinence procedures in women, with some authors reporting an incidence as high as 25% (Parnell et al, 1984; Galloway et al, 1987; Lose et al, 1987; Eriksen et al, 1990). Chronic groin pain and dyspareunia are also recognized risks of these procedures (Galloway 1987; Eriksen 1990). For example in a study that assessed the Burch colposuspension in 65 women at 1.5 years and 155 women at 4.5 years, late complications in these 220 women included cystocele in 18, rectocele in 32,

enterocele in 35, dyspareunia in 6, and groin or suprapubic pain in 15 (Demirci et al, 2001). In one study, 5% of women required removal of one or more permanent sutures following endoscopic bladder neck suspension (Jarvis 1994).

The recently published SISTEr trial represents the largest multicenter RCT comparing traditional autologous sling to Burch colposuspension (Albo et al NEJM 2007). 655 women were followed for 24 months. Success defined as no self- reported symptoms of SUI, a negative stress test and no retreatment for SUI was reported to be 66% versus 49% in the pubovaginal sling group versus the Burch group. Average blood loss for each procedure was 229ml and 238 ml respectively, and average operating times were 136 and 138 minutes respectively. Serious adverse events were reported in 13% and 10% of cases, respectively. Wound complications occurred in 25% of the total population, with 4% requiring surgical re-intervention. 3% of the patients randomized to a Burch colposuspension sustained a bladder injury.

Two of the more commonly recognized risks of traditional anti-incontinence procedures are prolonged voiding dysfunction and declining long term cure of incontinence of the procedures. In the SISTEr trial voiding dysfunction was reported in 14% of women undergoing the pubovaginal sling with six percent requiring surgical revision for persistent voiding dysfunction (Albo et al NEJM 2007).

The E-SISTEr trial reported on the five and seven year continence rates for women following the SISTEr trial. In this prospective observational study, the primary outcome of continence status was defined by a composite measure consisting of no symptoms of urinary incontinence on a 3-day voiding diary, no self-reported stress urinary incontinence symptoms on the MESA (Medical, Epidemiologic, and Social Aspects of Aging Project) questionnaire (response of rarely or never for each stress-type symptom) and no surgical re-treatment for SUI (Brubaker et al J Urology 2012). Urinary continence rates from the SISTEr to E-SISTEr studies decreased during a period of 2 to 5 and to 7 years postoperatively from 42% to 24% to 13% in the Burch group and from 52% to 34% to 27% in the sling group, respectively (Richter et al J Urology 2012; see Figure 2, Brubaker et al, 2012).

In the study by Demirci, the overall cure rate for the Burch colposuspension was 87.7% at 1.5 years and 77.4% at a mean 4.5 years of follow-up, and the symptom-free cure rate declined 83.9% for 3, 76.2% for 4, 75% for 5 and 68% for 6 years. (Demirci et al, 2001). The authors surveyed the literature and found that the overall data were consistent with the conclusion that cure rates with Burch decline

over time: Van Geelen et al. 1988 reported an objective cure rate after 3 months of 100%, at 1-2 years it was 85%, and 5 years after the procedure only 75.8% of the women were symptom-free; Thunedborg et al. 1990 reported a complete cure rate of 78.6% for 6 years; Kinn 1995 reported 78% for 5 years; Eriksen et al. 1990 reported 67% for 5 years, Lebret et al. 1997 reported 64% for 5 years; Kjolhede and Ryden 1994 reported 63% for 6 years; and finally Christensen et al. 1997 reported 33%. In a more recent study, Kjolhede reported on 190 women who underwent an open Burch colposuspension (2005). At 14 years, 56% demonstrated significant urinary incontinence, while only 19% of women remained completely dry.

Traditional anti-incontinence procedures are based upon older theories regarding the pathophysiology behind stress urinary incontinence. These theories focused on the pressure transmission between the increased abdominal pressure (i.e. during a cough or sneeze) and a simultaneous reduction in in urethral closure pressure, which results in stress leakage (Einhorning 1961, DeLancey, 1994). More recent investigations on the pathophysiology of stress urinary incontinence demonstrated the importance of mid-urethral support, provided by the pubo-urethral ligaments, and the functioning elasticity of the anterior vaginal wall which effectively transmits the contractions of the pubococcygeous and levator ani muscles to effect the separate closure of the urethra and bladder neck. A series of experimental investigations led to an alternative understanding of the urethral closure mechanism in women, that required the interaction between the suburethral vaginal wall, pubourethral ligaments and pubococcygeous muscles. These discoveries became known as the “Integral Theory” (Petros 1990, 1993). The Integral theory represented a paradigm shift away from traditional views, and as such, created the opportunity for a new surgical approach to stress urinary incontinence.

The desirability of a new surgical approach to female stress incontinence became self-evident in the 1980’s and early 1990’s. Stress urinary incontinence is a highly prevalent disorder amongst adult women, and surgical management is often first line therapy. Traditional approaches had significant perioperative morbidity, and were often associated with prolonged voiding dysfunction, and suboptimal long term results. The two “gold standard” procedures back then – the Burch Urethropexy and autologous fascial sling required general anesthesia, long operative times, and prolonged bladder drainage as previously discussed. Women were living longer and more active lifestyles and desired a high level of quality of life. Given the enormous scope and potential cost burden of SUI, there was a desperate need for a minimally invasive, outpatient surgical procedure to treat SUI. Finally, modern theories on the pathophysiology of SUI suggested that an

alternative procedure could address the most common risks of anti-incontinence surgeries, namely prolonged voiding dysfunction and poor long term durability.

Professor Ulf Ulmsten, and colleagues set about designing a new surgical approach that incorporated the new theory and specifically addressed the two most common shortcomings of the traditional anti-incontinence procedures – prolonged voiding dysfunction and poor long term cure rates. In addition, the new procedure considered more pragmatic needs, such as the ability to perform the procedure under local anesthesia as an ambulatory procedure with a minimally invasive approach which allowed for discharge to home on the same day as surgery without the need for prolonged Foley drainage. The procedure was also designed to address the full spectrum of the SUI disorder, and treat both primary cases of SUI as well as recurrent cases, as well as in combination with surgical procedures for the repair of pelvic organ prolapse. The initial procedure, known as the intravaginal slingplasty (IVS) was refined with respect to both the sling material used, and the instrumentation and these initial results were reported in 1996 (Ulmsten 1996).

The initial publication of the final TVT procedure reported on the results in 75 women who were operated on and followed for two years. The procedure was performed in an ambulatory setting under local analgesia with a mean operating time of 22 minutes; no significant postoperative complications (specifically, no erosion or rejection of the polypropylene mesh) with 92% of patients cured or significantly cured throughout the two year follow up period (Ulmsten 1996). The authors concluded that the new technique seemed both feasible and promising and prospective clinical trials were launched to further delineate the place of this technique in clinical practice.

Subsequent clinical trials demonstrated the appropriateness of the TVT procedure in treating the entire spectrum of SUI disorders, including its efficacy in treating primary stress incontinence, recurrent stress incontinence, mixed urinary incontinence and intrinsic sphincter deficiency, all with consistently excellent results (Rezapour & Ulmsten, 2001; Rezapour et al, 2001; Nilsson et al, 2001). This has established the appropriateness of the TVT procedure for treating a majority of women suffering from stress incontinence. For example, in a prospective long term follow up study in women with recurrent stress urinary incontinence followed for a mean of four years, 91% of patients remained cured or significantly improved, with no significant complications or long term postoperative voiding problems reported (Rezapour & Ulmsten, 2001).

By 2001, over 100,000 TVT procedures had been performed worldwide. Data on TVT continued to be published that confirmed the utility, efficacy and safety as earlier reported. Comparison of the TVT procedure to traditional procedures, such as the Burch colposuspension and autologous fascial sling demonstrated that the TVT has a cure rate equal to or better than the standard procedures and it is generally regarded as easier to learn and teach than both traditional and laparoscopic Burch procedures, with significantly shorter operative time, shorter hospital stays and recovery, and it is significantly more cost effective (Ogah Cochrane Review 2009). As a result of the design of the TVT, there is little pain and many patients do not even need pain medications. Moreover, most women can drive a car the next day, resume working within 2 days, and return to normal exercise in just one week, all of which lead to benefits to women's lifestyle and society.

Several of the TVT's design elements are desirable based on deficiencies in the prior procedures. The Burch colposuspension and autologous fascial slings utilize abdominal routes and suprapubic incisions that often resulted in wound infections, herniations, seroma and wound complications, as well as undesirable scarring. The harvesting of fascia lata from the thigh also led to secondary surgical site morbidity including wound complications, pain and nerve injury. As a result, there was a need for a design to avoid these complications by utilizing a vaginal approach, which was accomplished with the TVT. This is analogous and contemporaneous with the state of the art movement towards less invasive vaginal surgery in the field of gynecology such as the movement from abdominal hysterectomy to vaginal hysterectomy. Given the urethra's location above the anterior vaginal wall and its length of 3-4 cm, the TVT's trocar design and 1.1cm wide strip of mesh allowed easier placement under the midurethra using a much smaller incision than with prior procedures all the while avoiding opening up the retropubic space. The passage of needles in this area had been accomplished previously with the autologous slings but that procedure still required secondary large incision to the abdomen in order to tie off the sutures. Conversely, the design of the TVT allows a small upper passage, which can be sealed with Dermabond or a stitch at the site of trocar exit. It was also desirable to have an anchorless sling unlike prior art that led to pain, voiding problems, osteomyelitis and more exposures. The IFU directs that the tape is to be placed loosely. This can be carried out with the aide of a blunt surgical instrument like a Hagar dilator used as a spacer. Another benefit of the design is the ability to perform the procedure under local anesthesia as an ambulatory procedure. A further benefit is the ability to perform a cough stress test, which can be done whether the patient is under local or regional anesthesia.

The ease of use, teachability and learning curve of every single surgeon in Finland using TVT was demonstrated in a prospective, systematic training program, including the observed complications in 1,455 patients (Kuuva et al, 2002). The inventors thoughtfully and carefully developed a training program for surgeons that emphasized adherence to a standardized performance. These beneficial attributes and utility have led to the adoption of midurethral slings and specifically TVT as the preferred option for the treatment of stress incontinence by urologists and urogynecologists (Chughtai et al, 2013; Nager et al, 2012; ICS Stress Urinary Incontinence Fact Sheet 2013; Clemons et al, 2013; Rogo-Gupta et al, 2013; Wu et al, 2014).

The evolution of the TVT midurethral sling was based upon sound scientific and clinical principles. It incorporated the vaginal approach of the traditional pubovaginal sling and needle suspensions. However the critical modification was the placement of the sling at the level of the mid urethra in keeping with the Integral Theory rather than the bladder neck and the lack of a fixed anchor point to the abdominal wall fascia. This critical change dramatically reduced the complication of urinary retention and prolonged voiding dysfunction. The “bottom up” approach unique to the TVT design allowed for the precise placement of the mesh at the level of the midurethra. The importance of the mid urethral placement is evident by the fact that every subsequent development in anti-incontinence surgery in the past 15 years has centered on mid urethral placement for urethral stabilization.

It is important to recognize that the design of the TVT followed the path of many previous surgical techniques. Animal studies were performed in the 1980s to develop and test the feasibility of implanting permanent tape, which demonstrated low inflammatory responses in the implanted tissues. This led to human studies in the late 1980’s. Initial studies involving a removal of synthetic tape proved unsatisfactory and after three years of research, the use of a polypropylene mesh tape became universally accepted. Polypropylene material has be considered safe and effective as a surgical implant for over five decades, and has been used in a majority of surgical specialties including general surgery, cardiovascular surgery, transplant surgery, ophthalmology, otolaryngology, gynecology and urology. As an isolated thread, it is used widely as a permanent and durable surgical suture. As a knitted material, polypropylene mesh is the consensus graft material in a number of areas in the human body. Within the field of Female Pelvic Medicine, the use of knitted polypropylene, in the form of a macroporous, monofilament, light weight mesh tape has demonstrated long term durability, safety and efficacy up to 17 years (Nilsson et al. IUJ 2013; AUGS-SUFU Position Statement on Mesh

Midurethral Slings for SUI 2014). I have personally used it as my primary implant material in my patients for over 15 years in more than 3,000 patients, and have yet to observe a single case of mesh rejection, chronic foreign body reaction, mesh encapsulation or infection.

The TVT's design has provided for the ability and desirability to have a product with clinical data upon which to inform users of its utility. Both the material of the tape and its route of implantation have been assessed and are well known in the field. Before TVT, the earlier incontinence procedures had not been studied as robustly or broadly. In studies reporting on the longer term efficacy with these procedures, there was a high degree of loss to follow up. For example, in Alcalay et al, there was 70% loss to follow up in women who had undergone Burch colposuspension surgery in a 10-20 year longitudinal retrospective study (1995). Loss to follow up occurs over time as patients move, are unable to be contacted, do not wish to return for varying reasons or die.

In 1996, Black and Downs published the first systematic review assessing SUI surgery by identifying relevant literature, categorizing and assessing it methodologically, and synthesizing a coherent view. The methodological quality of the few prospective studies assessing colposuspension, autologous slings and needle suspension procedures was poor with only about 800 women randomized to these procedures that had been in use for decades (Black & Downs 1996). Among the author's conclusions it was observed that: in light of the methodological shortcomings of most evaluative studies, evidence about the effectiveness of surgery for stress incontinence is weak; there was little information on the value of sling procedures; and valid and reliable data on the frequency of complications following surgery are lacking, so the safety of the procedures is unclear. The need for well designed prospective studies to assess SUI procedures was advocated.

By comparison, the original retropubic TVT sling stands alone in the field of surgical urogynecology as the most extensively studied anti-incontinence procedure in history and over 2,000 scientific publications provide broad evidence supporting the use of polypropylene mid urethral slings as a treatment for SUI, with the majority of these publications using the TVT family of slings (Novara et al, 2007; AUGS-SUFU Position Statement on Mesh Midurethral Slings for SUI 2014; Ford Cochrane Review 2015). Its design and utility has stood the test of time and data showing its efficacy and safety have been replicated time and time again. It has been studied in virtually all types of patients, with and without medical co-morbidities, and across the entire spectrum of SUI disorders including primary and recurrent incontinence, mixed urinary incontinence, straightforward

SUI with a hypermobile urethra as well as intrinsic sphincter deficiency. Multiple randomized, controlled trials have been published comparing this approach to other established, non-mesh SUI procedures, producing the highest level of scientific evidence supporting its clinical effectiveness and high level of patient satisfaction, as well as demonstrating superior safety and efficacy. No other surgical treatment for SUI before or since has been subject to such extensive investigation.

At the present time, expert opinion and clinical practice guidelines from a wide group of subspecialty societies, such as the American Urogynecologic Society, American Urological Association, Society of Gynecologic Surgeons, Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction and the International Urogynecological Association advocate the mid-urethral sling as the standard of care for the surgical treatment of SUI and acknowledge that it represents a great advance in the treatment of this condition in women (AUA Position Statement on the Use of Vaginal Mesh for the Surgical Treatment of Stress Urinary Incontinence Oct. 2013; IUGA Position Statement on Mid-Urethral Slings for Stress Urinary Incontinence July 2014; Schimpf et al A systematic review and meta-analysis and SGS Recommendations 2014; AUGS-SUFU Position Statement on Mesh Midurethral Slings for SUI 2014). TVT and the mesh used in it are the dominant procedure and material assessed in incontinence studies, guidelines, metaanalyses and position statements. I belong to and have served in leadership roles to many of these organizations. These guidelines, analyses and position statements inform surgeons on the standard of care, the usefulness, utility, desirability of the TVT as well as its safety and do not support that TVT is unreasonably dangerous for its intended use.

The AUA in 2012 updated it 2009 guidelines for the surgical treatment of SUI. The peer-reviewed medical literature was systematically searched leading to over 7,000 publications that were systematically reviewed. 436 articles were meta-analyzed and an additional 155 articles were assessed regarding complication data in order for guideline generation, approval and dissemination. The AUA Guidelines established that the TVT is a suitable first line surgical option with established safety and efficacy (2009, 2012). As observed in the AUA's October 2013 Position Statement on the use of vaginal mesh for the surgical treatment of stress urinary incontinence, the utility and safety of TVT are well established:

> Suburethral synthetic polypropylene mesh sling placement is the most common surgery currently performed for SUI. Extensive data exist to support the use of synthetic polypropylene mesh suburethral slings for the treatment of female SUI, with minimal morbidity compared with alternative

> surgeries. Advantages include shorter operative time/anesthetic need, reduced surgical pain, reduced hospitalization, and reduced voiding dysfunction. Mesh-related complications can occur following polypropylene sling placement, but the rate of these complications is acceptably low. Furthermore, it is important to recognize that many sling-related complications are not unique to mesh surgeries and are known to occur with non-mesh sling procedures as well. It is the AUA's opinion that any restriction of the use of synthetic polypropylene mesh suburethral slings would be a disservice to women who choose surgical correction of SUI. Additionally, both the Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU) and the AUA support the use of multi-incision monofilament midurethral slings for the treatment of SUI in properly selected patients who are appropriately counseled regarding this this surgical procedure by surgeons who are trained in the placement of such devices, as well as the recognition and management of potential complications associated with their use.
>
> Multiple case series and randomized controlled trials attest to the efficacy of synthetic polypropylene mesh slings at 5-10 years. This efficacy is equivalent or superior to other surgical techniques. There is no significant increase in adverse events observed over this period of follow up. Based on these data, the AUA Guideline for the Surgical Management of Stress Urinary Incontinence concluded that synthetic slings are an appropriate treatment choice for women with stress incontinence, with similar efficacy but less morbidity than conventional non-mesh sling techniques.

IUGA's analysis reports that MUS like the TVT have been shown to be as effective as more invasive traditional surgery with major advantages (utility and desirability) of shorter operating and admission times, and a quicker return to normal activities together with lower rates of complications (IUGA July 2014 Position Statement on Mid-Urethral Slings for Stress Urinary Incontinence). This has resulted in MUS becoming the operation of choice in Europe, Asia, South America, South Africa, Australasia and North America for treatment of SUI with several million procedures performed worldwide.

Most recently, ACOG and AUGS conducted a systematic review of the medical literature and issued Practice Bulletin No. 155 Urinary incontinence in women (American College of Obstetricians and Gynecologists. Obstet Gynecol 2015;

126:e66–81). The following conclusions and recommendations based on good and consistent (Level A) evidence:

- Initial midurethral sling surgery results in higher 1-year subjective and objective cure rates than pelvic floor physical therapy in women with stress urinary incontinence.

- Synthetic midurethral slings demonstrate efficacy that is similar to traditional suburethral fascial slings, open colposuspension, and laparoscopic colposuspension. Compared with suburethral fascial slings, fewer adverse events have been reported with synthetic midurethral slings. Voiding dysfunction is more common with open colposuspension than with synthetic midurethral slings.

- There are substantial safety and efficacy data that support the role of synthetic mesh midurethral slings as a primary surgical treatment option for stress urinary incontinence in women.

It was also desirable to have a design that would be performed transvaginally as many other concomitant procedures were to be performed transvaginally, thus avoiding the need for an isolated and morbid abdominal procedure. Conversely the TVT has been shown to work efficaciously in tandem with planned abdominal repairs of prolapse. For example, in a study comparing Burch colposuspension or TVT performed concurrently with abdominal sacralcolpopexy in a cohort of 150 patients, TVT had significantly lower rates of post-operative SUI than Burch (10 versus 0, p=0.007) when performed with ASC (Patel et al IUJ 2009). Those who had a Burch procedure for SUI were more likely to have repeat surgery for SUI than those with a TVT procedure and there were no cases of TVT mesh exposures or sling revision.

It is also desirable to have a surgical treatment for SUI that can effectively and safely treat the broad spectrum of patients. In the past, procedures like the autologous fascial sling were reserved for some recurrent patients and those with ISD or stove pipe urethras. As noted earlier, the utility of TVT has allowed it to treat virtually all types of patients, both young and old, pre and post menopausal, those with primary and recurrent incontinence, as well as those with mixed incontinence and ISD (Cox et al, 2013). With a population that has seen rates of obesity rise, it is also desirable to have a treatment that addresses this cohort of patients and studies have also shown the TVT to be safe and effective in

overweight and obese patients (Osborn 2013). Greer et al. conducted a systematic review and meta-analysis and found TVT to be a safe and effective option in obese patients (2008). A cure rate of 81% was found in the obese cohort compared to 85% in the non-obese patients ($p<0.001$). While the result was statistically significant there was no clinically significant difference. The rate of bladder perforation favored the obese cohort (1.2% versus 6.6% in the non-obese cohort, $p=0.015$).

The design of the TVT has been found to lead to better efficacy than other retropubic slings, both intravaginal slingplasty (IVS; OR = 0.47; p = 0.007) and suprapubic arc (SPARC; OR from 0.53 to 0.56 according to the different evaluated end points) (Novara et al, 2007). While some, like Dr. Blaivas, have criticized the bottom up approach, Ogah et al compared these two approaches in a Cochrane review and found that women who underwent TVT's bottom-up approach had significantly fewer bladder perforations (4.7% vs 8.5%, RR 0.55, 95% CI 0.31-0.98), fewer vaginal tape erosions (0.7% vs 3.5%; RR 0.27, 95% CI 0.08-0.95) and reported significantly higher subjective (85% vs 77%; RR 1.1, 95% CI 1.01-1.2) and objective cure rates (92% vs 87%; RR 1.06, 95% CI 1.01-1.11) (2009).

Additionally, the results of several Cochrane reviews and meta-analyses establish the utility of the TVT and its design compared to other procedures (Cox et al, 2013):

Table 1 | Meta-analyses of midurethral slings versus traditional procedures for stress urinary incontinence

Study	Comparison	Subjective success at 12 months	Objective success at 12 months
Rehman *et al.* (2011)[26]	Pubovaginal fascial sling vs midurethral sling	Equal success ($n=693$) RR 0.97 (95% CI 0.78–1.20)	Equal success* ($n=160$) RR 1.29 (95% CI 0.45–3.71)
Novara *et al.* (2010)[27]	Midurethral sling vs Burch colposuspension	Equal success ($n=400$) OR 0.79 (95% CI 0.52–1.21; $P=0.27$)	Favoured midurethral sling ($n=528$) OR 0.38 (95% CI 0.25–0.57; $P=0.0001$)
Novara *et al.* (2010)[27]	Midurethral sling vs pubovaginal sling	Equal success ($n=281$) OR 1.28 (95% CI 0.74–2.23; $P=0.38$)	Equal success ($n=473$) OR 0.8 (95% CI 0.51–1.26; $P=0.35$)
Ogah *et al.* (2009)[4]	Midurethral sling vs pubovaginal sling	Equal success ($n=599$) RR 1.03 (95% CI 0.94–1.13)	NR
Ogah *et al.* (2009)[4]	Midurethral sling vs open Burch colposuspension	Equal success ($n=729$) RR 0.96 (95% CI 0.90–1.03)	Equal success ($n=468$) RR 1.04 (95% CI 0.94–1.14)

*At >12 months. Abbreviation: NR, not reported.

Table 2 | Meta-analyses of midurethral slings versus laparoscopic Burch procedure

Study	Comparison	Follow-up (months)	Subjective success	Objective success
Ogah *et al.* (2009)[4]	Midurethral sling vs laparoscopic Burch colposuspension	12	Equal success ($n=434$) RR 1.11 (95% CI 0.99–1.24)	Favoured midurethral sling ($n=513$) RR 1.15 (95% CI 1.06–1.24)
Dean *et al.* (2006)[32]	Laparoscopic colposuspension vs midurethral sling	18	Equal success ($n=327$) RR 1.12 (95% CI 0.98–1.29)	Favoured midurethral sling ($n=534$) RR 1.16 (95% CI 1.07–1.25)

Table 3 | Meta-analyses of different approaches for midurethral sling insertion

Study	Comparison	Follow-up (months)	Subjective success	Objective success
Ogah *et al.* (2009)[4]	Bottom-up vs top-down (retropubic)	5.5	Favoured bottom-up (n=492) RR 1.1 (95% CI 1.01–1.2)	Favoured bottom-up (n=636) RR 1.06 (95% CI 1.01–1.11)

Table 4 | Meta-analyses of retropubic versus transobturator midurethral slings

Study	Comparison	Follow-up (months)	Subjective success	Objective success
Novara *et al.* (2010)[27]	Retropubic vs transobturator	12	Equal success (n=1,736) OR 0.97 (95% CI 0.75–1.24; P=0.8)	Favoured retropubic (n=3,186) OR 0.8 (95% CI 0.65–0.99; P=0.04)
Latthe *et al.* (2010)[40]	TVT-O™ vs TVT™	6	Equal success (n=1,809) OR 1.06 (95% CI 0.85–1.33; P=0.03)	Equal success (n=1,809) OR 1.03 (95% CI 0.77–1.39; P>0.05)
Latthe *et al.* (2010)[40]	Transobturator vs TVT™	6	Equal success (n=889) OR 1.16 (95% CI 0.83–1.60; P>0.05)	Equal success (n=889) OR 0.94 (95% CI 0.66–1.32; P>0.05)
Ogah *et al.* (2009)[4]	Transobturator vs retropubic	12	Equal success (n=1,381) RR 1.00 (95% CI 0.96–1.05)	Favoured retropubic (n=2,434) RR 0.96 (95% CI 0.93–0.99)
Sung *et al.* (2007)[41]	Transobturator vs retropubic	12	Equal success (n=427) OR 0.85 (95% CI 0.38–1.92)	NR

Abbreviation: NR, not reported.

Ogah et al in the Cochrane review found that minimally invasive synthetic suburethral sling operations and in particular the TVT which was the most studied appeared to be as effective as traditional suburethral slings [8 trials, n=599, risk ratio (RR) 1.03, 95% confidence interval (CI) 0.94--1.13] but with shorter operating time and less postoperative voiding dysfunction and de novo urgency symptoms (2011). Similar results were reported in the Cochrane Review concerning traditional suburethral slings that assessed 12 randomized controlled trials (Rehman et al, 2012). Novara et al reported similar cure rates but traditional suburethral slings had more storage lower urinary tract symptoms (LUTS) (OR: 0.31; CI: 0.10–0.94; p = 0.04) and had a higher reoperation rate (OR: 0.31; CI: 0.12–0.82; p = 0.02) (2010). The recent SGS systematic review and meta-analysis found for pubovaginal slings vs MUS, metaanalysis of subjective cure favored MUS (OR, 0.40; 95% CI, 0.18 - 0.85) and as a result the MUS was recommended. (Schimpf et al, 2014).

TVT appeared to be as effective as open retropubic colposuspension (subjective cure rate at 12 months RR 0.96, 95% CI: 0.90--1.03; at 5 years RR 0.91, 95% CI: 0.74--1.12) with fewer perioperative complications, less postoperative voiding dysfunction, shorter operative time, and hospital stay but significantly more bladder perforations (Ogah et al 2011). Similar results were seen in the Cochrane Review concerning open retropubic colposuspension (Lapitan & Cody 2012). Novara et al in a meta-analysis found that patients receiving midurethral slings, predominately TVT (7 out of 8 studies included), had significantly higher overall (odds ratio [OR]: 0.61; confidence interval [CI]: 0.46–0.82; p = 0.00009) and objective (OR: 0.38; CI: 0.25–0.57; p < 0.0001) cure rates than those receiving

Burch colposuspension (2010).

Objective cure is significantly better for TVT compared to laparoscopic colposuspension (RR 1.15, 95% CI: 1.06 - 1.24), subjective cure is similar (RR 1.11, 95% CI: 0.99 - 1.24), but the TVT has significantly less de novo urgency and urgency incontinence, shorter operating time, hospital stay, and time to return to daily activities (Ogah et al 2011). Dean et al conducted a systematic review of TVT versus laparoscopic colposuspension and also found that objective success favored TVT and subjective success was equal (2006). There are several disadvantages of the laparoscopic Burch that have led to a reduction in its use in institutions including the fact that it is not easily learnt by surgeons due to the steep learning curve required for laparoscopic suturing and it requires general anesthesia, abdominal entry, pneumoperitoneum, and three or four abdominal incisions, all of which carry additional morbidity (Jelovsek et al, 2008).

There are more long term studies with 5 to 10 to 17 years follow up with the TVT that document its efficacy, with continence cure and improvement in the 80-90% range, and safety than any other surgery (Liapis et al, 2008; Nilsson et al, 2008, 2013; Olsson et al, 2010; Groutz et al, 2011; Heinonen et al, 2012; Serati et al, 2012; Svenningsen et al, 2013; Laurikainen et al, 2014; Tommaselli et al, 2015).

The TVT sling has revolutionized the treatment of SUI for women throughout the world. It has been adapted as the gold standard for its treatment. While the traditional Burch and vaginal swings are still appropriate in a select group of patients, randomized controlled trials and the highest form of evidence have demonstrated that the TVT is associated with slightly higher success rates, better long term durability and less associated morbidity. Polypropylene midurethral slings and in particular the TVT, which is the most studied MUS with the longest track record, is considered the accepted gold standard at the present time for the treatment of female stress incontinence due to its utility, usefulness and desirable attributes, as well as its well assessed, positive safety profile (Cox et al, 2013).

B. Safety of the design of the TVT.

The risks associated with the TVT procedure are not unique. Most of the surgical risks are common to anti-incontinence procedures as a group (Chahila 1999; AUA SUI Guideline 2012; AUA 2013 Position Statement; Schimpf et al, 2014). The risks of stress incontinence surgery can vary from minor to severe and are known to surgeons who are the intended users of the TVT. All surgery including surgery

to treat stress incontinence is per se dangerous and requires due care. Surgeons are taught this in medical school, residency and further training and complications are known to occur with all surgeries. That is a fundamental tenet of surgery. There are numerous elemental, known risks of vaginal and stress incontinence surgery such as injury to organs, vessels, nerves and adjacent tissue, infection, bleeding, pain including dyspareunia and pelvic pain, wound complications, tissue contraction and scarring, voiding problems, recurrence, and the need for reoperation. Surgeons know of these risks from their basic surgical training and they are obvious to the intended user of TVT given our surgical training and expected knowledge. Risks of the SUI surgeries are a part of the major gynecologic, urologic and urogynecologic textbooks and risks are also tested during training and are a part of specialty and subspecialty certification. For example, it is obvious to a pelvic floor surgeon who performs incontinence surgeries that use of surgical instruments like a TVT trocar can lead to organ, vessel and nerve damage. All stress incontinence surgeries can lead to wound complications as earlier referenced such as granulation tissue, wound herniation, dehiscence, and suture, mesh and biologic graft erosion, which are obvious given our training and use of instruments and materials during surgery. All of these risks have long been reported in the medical literature and are expected to be known by surgeon users. They are analyzed and discussed in professional society analyses, reviews, guidelines and statements, as well as the FDA public health notice of 2008, the 2011 FDA advisory committee proceedings, and the FDA's 2013 statement concerning midurethral slings. Notably, the Burch colposuspension and autologous slings do not have an IFU and Professional education like is present for the TVT, which supplement all of the other sources of the surgeon's knowledge. The IFU and Professional education for the TVT are clear, useful and adequate to describe the procedure and potential risks. Risks of SUI surgery are obvious to surgeons and as surgeons, we are expected to be aware of the risks in light of our education, training and experience.

Intraoperative injuries include perforation of the bladder, urethra, bowel, blood vessels or vaginal injury. Bladder injury has been reported to occur in 5.0 – 5.5% of cases and occurs with the retropubic placement of the trocars. It is easily detectable by cystoscopy, which has always been a required step of the TVT procedure. Intra-operative hydrodissection has always been advocated to reduce this risk. Overall, the risk of bladder injury with a retropubic TVT is similar to that of a Burch suspension or pubovaginal sling. Unlike bladder injuries that occur at the time of a Burch urethropexy, these injuries heal spontaneously and do not require prolonged Foley drainage. In our practice, the risk of bladder injury has been reduced to 1% with experience. Urethral injury has been reported to occur at

a median rate of 0.88% (Daneshgari 2008). Again, the standardized procedure of the TVT has emphasized periurethral hydrodissection and careful blunt dissection and cystoscopy. Bowel injury is uncommon, and is estimated to occur in 0.34% of retropubic slings compared to an estimated 3.13% of Burch procedures (Schmipf et al, 2014). Mean operative blood loss is minimal compared to the Burch urethropexy (Albo et al 2007 SISTEr and Albo et al 2012 TOMUS trials). Surgical hemorrhage occurs in less than 2% of TVT cases.

The recent systematic review conducted and published by the Society for Gynecologic Surgeons Systematic Review Group (Schimpf et al, 2014) reported that mid-urethral slings results in lower rates of perioperative adverse events such as blood loss, postoperative pain, operating room time, hospital stay, bowel injury, DVT, wound infections and hematomas compared to the Burch procedure. This recommendation was based upon level 1C evidence. Comparing absolute complication rates between pubovaginal slings and the retropubic TVT sling, the TVT sling resulted in lower rates of operating room time, blood loss, transfusion, wound infection, retention, OAB symptoms, DVT, and hospital stay, whereas pubovaginal slings had lower rates of urinary tract infection and vaginal perforation. A metaanalysis of adverse event information showed no significant difference in return to the OR for sling erosion, but favored the mid-urethral sling for better subjective cure.

Despite concerns that mid-urethral sling procedures can be anticipated to result in significant number of complications that would require surgical revision, the probability of surgical re-intervention has already been well studied. Data from numerous studies, including national and regional closed systems like the Kaiser Permanente HealthConnect Clarity database has consistently demonstrated low rates of perioperative complications and reoperation rates. Several well conducted studies and meta-analyses of different designs show that the need to reoperate for sling revision / removal following a TVT occurs in about 2.5 - 3.5% of patients studied out to 10 years. (Welk et al JAMA Surg 2015; Unger et al IUJ 2015; Schimpf et al, 2014; Laurikainen et al 2014; Jonsson Funk et al, 2013; Svenningsen et al, 2013; Nguyen et al, 2012; Ogah et al, 2009; Novara et al 2008). My search of the medical literature has revealed consistency in the low rates of complications requiring surgery reported in reliable scientific data. Case reports and case series cited by plaintiffs' experts like the paper by Abbott et al 2014 are deficient in numerous respects, biased, of limited evidence value and do not have a denominator thus they cannot be said to apply to the general population of TVT users or patients ("Perhaps most importantly, there is no denominator for the total number of patients who underwent an SUI or POP procedure with synthetic mesh.

Thus, we can make no comments about the rate at which such complications occur."). Even in that case series of 347 patients who sought care for complications, it was reported that less than half of the sling only cohort, 23.3%, underwent two or more reintervention surgeries. Thus the need for multiple reintervention surgeries was not more likely than not even in this biased and confounded cohort. It was also observed that those women with complications after a sling-only procedure were treated more often with medical treatment first and rarely required surgical reintervention. These data do not support the claims that TVT places a women at a significant risk of long term, chronic complications or the need for reoperation as plaintiffs' experts suggest.

The TVT design allows for the tape to be placed loosely, with space, to minimize the risk of voiding dysfunction and retention. If there is retention or voiding difficulties the tape can be pulled down with access through tiny ¼ inch incision and 70% of patients remain continent. Conversely addressing voiding dysfunction following a Burch is much more difficult and risky as it requires a second laparotomy procedure. Revision of a Burch relative to a TVT sling is a more morbid procedure.

Dyspareunia/vaginal pain with TVT is rare and less than that seen with Burch and fascial sling (Schimpf et al, 2014; AUA Updated SUI Guidelines 2012). Zyczynski et al reporting on the planned secondary analysis on TOMUS trial on sexual activity and function two years after MUS surgery (including TVT). Pain with sexual intercourse decreased from 38% at baseline to 27%. Overall sexual function improved significantly. Persistent pain in the groin or thigh occurs infrequently with the retropubic TVT procedure, ranging from 1.5% to 2.6% (Laurikainen 2007, Latthe 2010), similar to what has been reported with the Burch procedure. This problem can be effectively managed with either conservative management or partial excision of the tape (Duckett & Baranowski 2013; Duckett & Jain 2005). Concerns that the TVT leads to permanent dyspareunia and a negative impact in sexual function is inconsistent with these data.

Vaginal exposures occur at a rate of about 1-3% and are manageable. (Schimpf et al, 2014; AUA Updated SUI Guidelines 2012; Cox et al 2013; Ogah et al Short Cochrane Review 2011; Novara et al 2008) This is typically the result of a breakdown or opening of the vaginal incision after surgery. In most cases, the vagina can be reclosed over the mesh. However in some cases, the exposed portion of mesh is excised and the vaginal tissue closed, which is usually performed as an outpatient under local analgesia and light sedation. As earlier noted, wound complications occur at higher rates with the Burch and autologous

fascial sling. (Schimpf et al, 2014; AUA Revised SUI Guidelines 2012; Albo et al, 2007).

The long term safety of the TVT is well established based upon numerous intermediate and long term studies. Tamussino reported on the results of the Austrian registry of 2795 patients who had undergone a TVT sling with or without concomitant prolapse repair (Tamussino et al, 2001). Within this cohort only 2.4% required reoperation for reasons related to the tape. The most common reason being surgical revision for voiding dysfunction. There were 12 loosened, 3 removed, and 15 cut. There were no reported cases of surgical revision for erosion, pelvic pain, dyspareunia or vaginal scarring.

Novara et al conducted a systematic review of the literature in 2007 to evaluate the complication rates of TVT to traditional incontinence procedures such as the Burch colposuspension. The authors concluded that the TVT had a lower risk of reoperation than the Burch colposuspension and a similar complication rate compared to pubovaginal sling. An analysis included over 30 non-randomized studies with follow up duration over 24 months and reported overall vaginal erosion rate of 1.1%, bladder erosion rate of 0.8% and a reoperation rate of 3.2%.

Jonsson Funk et al interrogated the Thomson Reuters MarketScan® Commercial Claims and Encounters (CC&E) and Medicare Supplemental Coordination of Benefits database from 2001–2010 extracting data on 188,454 eligible women who underwent an index sling. The 9-year cumulative risk of sling revision/removal was 3.7% (95%CI 3.5, 3.9). At one year, this risk was already 2.2% and then increased to 3.2% at four years before plateauing. Regarding the indication for the sling revision/removal, a greater proportion was due to mesh erosion compared to urinary retention, with a 9-year risk of 2.5% (95%CI 2.3, 2.6) for mesh erosion versus 1.3% (95%CI 1.2, 1.4) for urinary retention. This large study demonstrates that the risk of reoperation plateaus early and decreases in the long term and therefore is inconsistent with plaintiffs' experts' claims that women have a significant risk of multiple erosions over their lifetime.

In another large, long term cohort, Svenningsen et al 2013 reported on 483 women from the Norwegian National Incontinence Registry Database with a median follow-up of over 10 years. Objective cure rate was 89.9%, subjective cure rate was 76.1 %, and 82.6 % of the patients stated they were "very satisfied" with their surgery at 10 years. Of note, only 2.3 % of the women had undergone repeat SUI surgery. The total number of exposures was 4 (0.8 %) for the whole 10-year period. The surgical method used was simple excision of the exposed part of the

tape and then re-suturing of the vaginal wall after mobilizing the edges of the defect.

Nguyen et al 2012 reported on 4,142 women (mean age 57 years [standard deviation 12.2], median parity 3 [interquartile range 1–4], median body mass index 28 [interquartile range 25–32]) of whom 3,747 (71%) underwent implantation of a sling to treat SUI with TVT having the most patients. Mesh-related reoperations after sling procedures were performed in about 2.2% of the patients: for voiding dysfunction or urinary retention (49 of 3,747 [1.3%]), vaginal mesh erosion (30 of 3,747 [0.8%]), urethral erosion (3 of 3,747 [0.08%], and pain (1 of 3,747 [0.04%]). Multiple excisions for persistent mesh erosion occurred in only 2 of 30 vaginal mesh erosion cases (6% of exposures versus 0.06% of the cohort of 3,747 sling patients). Vaginal mesh excision rates did not differ significantly between sling approaches (P=.93) or between manufacturers (P=.73).

Laurikainen et al 2014 reported the results of a five year randomized controlled trial comparing TVT and TVT-O in which 268 women (95%) were assessed according to the protocol. No woman had any sign of tissue reaction, erosion, or tape protrusion at their 5-yr follow-up. Additionally, none of the women in the TVT group needed surgery for retention or exposure or reported problems with the tape during the study. New-onset urgency incontinence was seen in 3.1% (4/131) in the TVT group, while more than 80% of the women were cured of their preoperative urgency symptoms. These findings suggest that the risk of developing urgency symptoms with or without leakage after TVT is very low and that actually, as reported earlier by Palva and Nilsson, surgery with TVT can cure urgency symptoms (IUJ 2011). Overall, objective cure rate was 84.7% in the TVT group and 86.2% in the TVT-O group and subjective treatment satisfaction was 94.2% in the TVT group and 91.7% in the TVT-O group, with no difference between the two. 92.6% of TVT patients would recommend TVT to a friend.

Unger et al found a 2.7% rate of surgical intervention in 3,307 women who underwent sling placement with a median time from the index to the revision surgery of 7.8 months (IUJ 2015). Voiding symptoms and urinary retention were the most commonly reported indications for revision, followed by mesh erosion. Very few (0.2%, 7/3,307) had pain/dyspareunia as a reason for intervention. The type of sling was not associated with the need or indication for revision. Approximately 70 % of patients in this study reported either partial or complete improvement of their symptoms after revision surgery. All patients who had undergone revision for pain symptoms of had either partial or complete improvement.

In a recent study that analyzed 59,887 patients who received a synthetic sling for SUI, 2.2% of patients underwent operative intervention for mesh complications and the overall 10 year cumulative rate of complications was also low, at about 3% (Welk et al JAMA Surg 2015). These results are consistent with the above. The authors also observed that the majority of reinterventions occurred in the first year, which is also consistent with Jonsson Funk et al, Nguyen et al, Unger et al, and my clinical experience. These interventions are mostly due to sling placement and voiding difficulties.

Overall, the data from these high quality long term registries do not support the claims that TVT places a women at a significant risk of long term, chronic complications or the need for reoperation as plaintiffs' experts suggest.

It is well established that women who suffer from pelvic floor disorders such as stress urinary incontinence and pelvic organ prolapse have weakened or structurally altered connective tissue, including deficiencies in their collagen matrix (Norton P et al, 1992; Ulmsten 1987; Gilpin 1989; Cosson et al, 2003). Observations that female SUI is the result of deficient pubourethral ligaments and paraurethral tissue was a critical element of the Integral Theory which led to the development of the TVT procedure (Ulmsten et al, 1987; Falconer et al, 1998). This concept is further supported by the work of John DeLancey (1994).

Another area of criticism has centered on the choice of Prolene polypropylene in the TVT. However, the use of reinforcing materials in the surgical management of these disorders has increased significantly in the past 30-40 years within the field of female pelvic floor reconstruction. While both biologic and synthetic material have been proposed for this application, for the most part, the use of biologic xenografts and allografts has been shown to be unsatisfactory (Fitzgerald et al BJU, 1999; Huang, 2001; Fitzgerald 1999), and their clinical use has substantially declined since the introduction of synthetic mesh slings. Graft extrusion is still a recognized complication of biologic graft slings (Chung 2002). Therefore, many surgeons have focused on the use of synthetic implants to compensate for damaged tissue and in hopes of providing long term durable results.

The use of synthetic mesh in pelvic floor surgery was widely established since the 1970s (Lane 1962; Morgan 1970). Polypropylene material has be considered safe and effective as a surgical implant for over five decades, and has been used in a majority of surgical specialties including general surgery, cardiovascular surgery, transplant surgery, ophthalmology, otolaryngology, gynecology and urology. As

an isolated thread, Prolene polypropylene is used widely as a permanent and durable surgical suture. As a knitted material, polypropylene mesh is the consensus graft material in a number of areas in the human body. Specifically, type 1 mesh is universally recognized as possessing the highest biocompatibility with the least propensity for infection. (Ford Cochrane Review 2015). Differences in their efficacy and complications are likely to be due to several factors including the different knits and weaves of the various tape materials, their biomechanical properties and histological biocompatibility. Pore size affects the inflammatory response and resultant connective tissue formation within and into the mesh, and the rearrangement of materials such as collagen within the mesh structure. Macroporous meshes (pore size in excess of 75 μm) easily allow macrophages, leukocytes, fibroblasts, blood vessels and collagen to transverse the pores: thus macroporous meshes promote tissue host ingrowth with resultant biocompatibility and low risk of infection (Amid 1997).

Even prior to the development of the TVT device, the use of synthetic mesh slings for treatment of incontinence was well described (Morgan 1970; Nichols DH 1973; Stanton 1985). The earliest prototypes for the TVT device critically evaluated the use of a variety of these synthetic materials, such as Mersilene and Gortex before the Prolene mesh found higher exposure rates (Petros 2015; Ulmsten et al, 1996). These authors also reported that these materials (Gore-Tex, Teflon, Mersilene) were associated with significant inflammatory reaction in paraurethral tissues and caused a significant amount of tape rejection. (Falconer et al, 2001).

It is widely recognized that the creators of the TVT developed the procedure through thoughtful and extensive clinical documentation and scientific examination. The choice of a type 1, macroporous, monofilament polypropylene mesh became the obvious choice for the TVT device, based upon the experience referenced above. This material has been repeatedly demonstrated to offer the desired mechanical properties of durability and elasticity as well as excellent host tolerability and lack of evidence of rejection. Type 1 macroporous mesh with pore size > 75 microns allows for infiltration by macrophages, fibroblasts, blood vessels in angiogenesis and collagen fibers (Amid 1997).

The Prolene mesh utilizes a large pore size for a small 1.1cm wide strip of tape and promotes mechanical anchorage with collagen. The initial TVT trials with Prolene mesh showed no adverse reaction like impaired wound healing or tape rejection (Ulmsten et al, 1998). Biopsies of the paraurethral connective tissues two years after a TVT procedure confirmed no evidence of tissue reaction. (Falconer et al, 2001). While there was a significant foreign body reaction seen with Mersilene,

there was a minimal inflammatory without a significant change in collagen solubility. Nilsson et al reported the 7-year and then 11-year follow up of a prospective observational cohort of 90 women who underwent the TVT procedure. In addition to reporting only a 3% failure rate, there were no long-term adverse events, including mesh erosion (Nilsson et al, 2004, 2008). These results have also been independently substantiated by Tamussino et al 2001, who has described the Austrian registry of 7000 TVT operations in which there were no cases of mesh rejection or intolerance reported, as well as other studies mentioned in this report. The pore size of the of the small mesh tape in TVT is the largest among the SUI tapes. It is optimal for its intended use, to treat SUI on a long term basis and the long term studies and voluminous data show this.

The choice of a macroporous, monofilament Prolene polypropylene mesh tape as the most suitable material is supported by strong clinical data (Cox et al, 2013; Ogah 2011, monofilament tapes (of which TVT mesh predominates) had significantly higher objective cure rates (RR 1.15, 95% CI: 1.02--1.30) compared to multifilament tapes and fewer tape erosions (1.3% vs. 6% RR 0.25, 95% CI: 0.06--1.00)). Synthetic prostheses made of polypropylene remains the most promising material for this use (Cosson et al, 2003). Both the FDA and AUGS/SUFU, as well as the AUA and IUGA, have specifically determined that the safety and effectiveness of polypropylene multi incision midurethral slings is well established. (FDA Considerations about surgical mesh for SUI 2013; AUGS-SUFU Statement 2014; AUA Position Statement on the Use of Vaginal Mesh for the Surgical Treatment of Stress Urinary Incontinence Oct. 2013; IUGA Position Statement on Mid-Urethral Slings for Stress Urinary Incontinence July 2014).

Among the polypropylene multi incision midurethral slings, Ethicon's TVT sling has the most data and longest follow up. There is no credible scientific evidence that a larger pore mesh like Ultrapro mesh used for prolapse, or Vypro, PVDF or other meshes used for hernia repair, which are larger applications, would work as well and over 17 years in the TVT design. What is known is that the size of the mesh is only 1.1 cm in width and the pore size for TVT is optimal in design for long term continence cure and a low rate of complications. (Cody 2015; Novara et al, 2008) As discussed earlier, the sheath is an important design feature and I have reviewed materials that document that the Monocryl component can stick to the sheath and lead to a breakdown of sling integrity upon sheath removal. There will always be a risk of exposure and erosion with any foreign material and there is no reliable scientific data that shows that increasing the pore size of TVT would increase efficacy or lower complications without impairing its utility including its established long term utility, durability, and safety.

There has also been a claim that the particles from the mechanically cut mesh can lead to complications like pain and erosion. This is speculation and without reliable scientific support. In my searches and review of the clinical literature, and my attendance at specialty meetings and conferences, this is not a concern and particle loss has not been identified by any reliable scientific clinical studies as a cause of complications. The material in any particles would be the same Prolene polypropylene material used in the mesh. As discussed above the tolerability and biocompatibility of this material in women is established. Prolene sutures are also used in much larger quantities in other surgeries and surgeons for decades have hand cut mesh in the operating room. The long term clinical studies on TVT which show its efficacy, durability and safety have used mechanically cut mesh and the literature from before and after 2007 when laser cut mesh became available do not demonstrate a difference in clinical effect based on whether the mesh is cut mechanically or with a laser. Both behave the same under physiologic conditions. Of course either can have particle loss and rope under misuse such as removing the sheath and stretching the tape as plaintiffs' experts suggest, but that is not how TVT mesh is designed to be placed in women nor is it consistent with the TVT IFU and Professional education. High levels of force can be placed on the tape with the sheath on and the tape is not altered. Photographs referenced by plaintiffs' experts of the tape being stretched on a machine without the sheath or the trocars are not transferable to placement of the tape at the time of surgery. Overall, the theory that particles from mechanically cut TVT lead to adverse clinical effects in patients in not supported by the medical literature or my clinical experience having placed thousands of these slings. In my practice, I prefer the mechanically cut TVT mesh due to they way it handles in the operative suite and due to my long history of its use. I have also used laser cut mesh for SUI and have discerned no clinically significant difference or effect. This is more of an aesthetic theory not born out by reliable scientific data and it has not been differentiated as clinically significant by any of the pertinent surgical societies setting forth guidelines and analyses.

Some have raised concerns about the possibility of an adverse host tissue response to type 1 polypropylene mesh tape. These opinions are based largely upon studies involving animal models or studies involving abdominal hernia repairs. Studies that have specifically evaluated the pelvic floor tissue response are limited to small case series, and often are typically to a subset of subjects that have chronically extruded mesh implants. It is important to recognize that animal studies are not directly transferable to human subjects, and that individual tissue responses at different anatomic locations are likely to differ. They are also, in my opinion,

inconsistent with the extensive clinical experience with the TVT device referenced throughout this report which have shown that adverse events such as impaired wound healing, infection, or rejection are rare events. Furthermore, it is inappropriate to extrapolate data involving sheets of mesh to the much smaller surface area of the TVT device, as there are data showing that the surface of the implant, the fewer intolerance reactions are observed (Norris 1996, Cosson 2003). Similarly, mesh weight is directly related to the amount of mesh material implanted, again, making it inappropriate to extrapolate data on mesh sheets to the TVT device. Moreover, there is no recognized weight classification for midurethral slings, which are only 1.1cm in width. Differences in mesh architecture is also likely to affect tissue response, making the applicability of many of the studies cited by the plaintiff's experts to be highly questionable and of limited scientific value in regards to TVT. The weight of the small mesh tape in TVT is optimal for its intended use, to treat SUI on a long term basis and the long term studies and voluminous data show this.

A claim has been made by plaintiffs' experts suggesting a possible association between synthetic MUS based on rodent studies where sarcoma formation was reported after implantation of sheets of polypropylene. After an extensive review of the existing literature, I have concluded that these assertions lack scientific validity. These opinions are founded upon a report from 1958, when Oppenheimer et al identified the development of various sarcomas in rats implanted with sheets of plastic film (Cancer 1958; 11:204–213). Of note, the latency times to cancer formation ranged from 7 months to two years in this study. Interestingly, in some previous animal models, it was noted that surface area, shape and surface morphology had an impact on the risk of sarcoma development, with perforated materials having lower risks than solid, flat films of material (McGregor et al, Eur J Cancer 2000; 36:307–313). More recent animal studies evaluating monofilament and multifilament polypropylene mesh implantation in the subcutaneous tissues of mice did not corroborate these findings, with no sarcomas identified during two years of follow up (Witherspoon et al, Br J Surg 2004; 91:368–372). Despite the widespread use of synthetic mesh in surgical procedures in humans over the past 50 years, there have been few reports of malignancy formation after implantation with prosthetic materials. These concerns have recently been addressed by Moalli et al and it was concluded that polypropylene, which has been used extensively in humans for over five decades, is not associated with carcinogenesis. (Moalli et al, 2014). As stated in the AUGS/SUFU Frequently asked questions by providers-Mid-urethral slings for stress urinary incontinence "There is no compelling evidence supporting human malignant transformation related to polypropylene despite the millions of individuals implanted with various forms of this material

span well over a half century world-wide." (AUGS-SUFU FAQs by Patients on Mid-urethral Slings for SUI March 2014). Type 1 macroporous, monofilament polypropylene has been found to be the most biocompatible biomaterial for use in the pelvic floor (Ford 2015).

With specific regard to synthetic midurethral slings and meshes used in pelvic floor support, there is no reliable scientific evidence to indicate that mesh induces malignancy. Several large observational series have now been published looking at synthetic MUS. King et al reported on 2,361 patients who underwent synthetic sling placement, and found one case each of bladder and vaginal cancer for an incidence of 0.08%, with mean follow up of 42 months (Urology 2014; 84:789–792). In a more recent series, Linder et al discovered only 2 cases amongst 2,474 who underwent polypropylene MUS placement (0.08%) with a mean follow up of 61.5 months (Int Urogynecol J. 2016 Feb 10. Epub ahead of print). In this study, 49 cancer diagnoses occurred before the date of sling placement. Thus the background rate of cancer in these patients was 2% (49 out of 2,474). This high background rate of cancer further demonstrates the lack of reliability in Plaintiffs' experts' position that polypropylene causes cancer in women when used for pelvic reconstruction. Notably, there are no epidemiologic data that show a statistically significant increased rate and risk of cancer with polypropylene MUS and meshes used in pelvic floor support compared to the expected population level data. Additionally, the Mayo Clinic group found that no local cancers were detected among the 302 patients (12 % of the cohort) with more than 10 years' follow-up.

Both groups concluded that given the histology, location, and expected background incidence of these cancer, that there was no evidence of an association between mesh placement with subsequent local cancer formation. In order to establish an association, between polypropylene mesh and cancer formation, it must be demonstrated by much more than case reports (Goldman et al, Int Urogynecol J. 2016; 27:345-6.)

Another claim has been made that the Prolene mesh in TVT is cytotoxic based on in vitro testing that accompanied the TVT 510k submission. It is notable that this information was presented to the FDA within the context of available human data that showed clinical efficacy and safety. The overall clinical data do not show that the mesh is cytotoxic in humans. If it were the mesh would not incorporate into the tissues and instead it would lead to abundant necrotic tissue formation and rejection, which is not seen in the literature. The randomized controlled trials, cohort studies and systematic reviews show excellent efficacy, safety and tolerability, which is the opposite of what one would expect to see if the mesh were

cytotoxic. Another concern raised has been the possibility that the polypropylene mesh used in mid-urethral slings degrades over time. Again, it can be pointed out that polypropylene, and specifically Prolene polypropylene, is a stable and well accepted biomaterial with an extensive use for over five decades as a biologic implant. These concerns seem to focus on reports that have detected "cracked surfaces" along portions of explanted synthetic mesh, visible only with very high scanning electron microscopy magnification, and the further hypothesis that these microscopic features could lead to adverse clinical outcomes. For example, the Clave et al paper reported surface cracking was observed in only one third of polypropylene monofilament explanted specimens that were available for analysis. However, according to the authors specific deteriorations correlating to implant material were not observed (Clave et al, 2010). The authors further acknowledge that they were unable to conform their hypotheses concerning potential degradation of PP include whether or not direct oxidation occurs in vivo. Additional limitations acknowledged were that they were unable to determine whether the mechanical properties were altered and they had not analyzed implants from non-pathologic states. In my opinion, the observations of surface cracking in a minority of specimens does not establish that degradation occurs and more importantly, that the mechanical and functional properties are in any significant way compromised. Finally, the authors state that they were unable to predict whether or not these changes could or do occur in non pathologic states. Again, the opinions expressed by sub-specialty societies such as AUGS and SUFU have dismissed these concerns by pointing out that they are not supported by extensive peer reviewed literature related to polypropylene mesh repair (AUGS-SUFU FAQs by Providers on Mid-urethral Slings for SUI March 2014). Moreover, my analysis of the data, including the numerous long term studies on TVT referenced in this report, leads me to conclude that the Prolene polypropylene in TVT does not degrade or if it did, that it has a clinically significant effect. Prolene polypropylene has been studied more than any other material for use as a sling and it is the best material as born out by the clinical data discussed in this report.

Also, it has been suggested by plaintiffs' experts that TVT can result in chronic inflammation or infection. However, there is no definitive scientific evidence to support this. The earlier referenced studies do not support these theories and the metaanalyses and systematic reviews show that infection of the mesh is exceedingly rare. For example, in the Norwegian National Incontinence Registry, which included 4,281 women who had a TVT operation, the infection rate was 0.7% (Dyrkorn et al, 2010). I have personally implanted over 2,500 TVTs and have seen no mesh infection. Importantly, contamination does not equate to infection. Concerns that bacteria adhere to the TVT tape during implantation and lead to

clinical infection is not supported by the broad base of high quality scientific papers on the worldwide TVT experience. (Ford Cochrane Review 2015) Even a study by one of plaintiffs' experts does not support this concern, as Klinge et al also reported in a rat model, that in vitro bacterial adherence occurs significantly less frequently with monofilament mesh compared to multifilament mesh and that the persistence of bacteria did not lead to a clinically higher rate of infection (Klinge 2002). Concerns regarding potential contamination of the mesh have been addressed in the design of the TVT device and are discussed in the next paragraph.

Another important design characteristic of the TVT device was the inclusion of a clear plastic sheath, which facilitated the placement of the sling in the correct position around the midurethra. The use of the sheath to facilitate tape placement and tensioning protects the tape from deformation while maintaining the strong adhesive forces that keep the tape in place once the sheath is removed. The incorporation of the sheath in the design transfers the load of forces during insertion, which prevents deformation of the mesh, and allows for smoother placement without dragging the tape through the tissues (Ulmsten et al, 1996). It also minimizes potential mesh induced trauma to the surrounding tissues during placement while maintaining the excellent tissue entrapment that occurs once the sheath is removed. Finally, the plastic sheath prevents the sling from becoming contaminated at the time of implantation.

Numerous level 1 randomized comparative trials have established the TVT sling as the most common surgical procedure for the treatment of SUI in the US and the developed world. This procedure has essentially replaced open and transvaginal suspension surgeries for uncomplicated SUI (AUGS/SUFU Statement 2014). Mesh mid-urethral slings are considered to be the current gold standard for stress incontinence surgery. A recent survey indicates that these procedures are used by >99% of the membership of the American Urogynecologic Society, the premier organization dedicated to the treatment of female pelvic floor disorders (Clemons et al, 2013). In addition to a proven track record of safety and efficacy, the mid urethral sling is associated with less pain, shorter hospitalization, faster return to usual activities and reduced health care costs compared to the other current options that have been used in the surgical management of stress urinary incontinence.

Potential substitute products for the retropubic TVT sling would include the second and third generation mid urethral slings, which were developed to address some of the concerns regarding the blind passage of the sling adjacent to the bladder through the space of Retzius. These endeavors led to the development of both the transobturator and single incision mini-slings. Several published trials and

metaanalyses referenced above have shown no clinical advantage of these alternative approaches over the retropubic TVT in terms of either reduced surgical complications, mesh erosion or improved outcomes. A recent observational study involving the MiniTape, mini-sling demonstrated a 20% mesh complication rate and only a 10% cure rate at two years (North et al 2009). Expert opinion and well designed clinical trials continue to favor the retropubic approach in cases of recurrent incontinence and in the presence of intrinsic sphincter deficiency. In my own clinical practice, I currently perform the retropubic TVT almost exclusively at the present time, despite the fact that I am well versed in the other two surgical approaches.

As previously discussed in this report, it has been suggested that biologic graft slings might eliminate some of the complications associated with synthetic mesh tapes. However the long-term durability of these procedures is lacking (Fitzgerald et al BJU, 1999, Huang, 2001; Fitzgerald 1999), and their clinical use has substantially declined since the introduction of synthetic mesh slings. Graft extrusion is still a recognized complication of biologic graft slings (Chung, 2002). Unlike TVT, rejection and dissolution are significant risks with allografts and xenografts. Allografts and xenografts also have to be irradiated or treated and there is a high rate of degradation seen with these materials. These materials also have risks of potential risk of virus and prion transmission and infectious disease transmission. Many patients do not desire to have grafts from pigs, cattle or cadavers placed in their bodies. Unlike the design of the TVT, there is a lack of consistency in the end product and cadaveric and xenografts also are not cost effective or readily available to treat the numbers of women who have SUI.

Dr. Blaivas has criticized the bottom up approach. However a meta analysis that compared these two approaches found that women who underwent the bottom-up approach had significantly higher fewer bladder perforations (4.7% vs 8.5%, RR 0.55, 95% CI 0.31-0.98), fewer vaginal tape erosions (0.7% vs 3.5%; RR 0.27, 95% CI 0.08-0.95) and reported significantly higher subjective (85% vs 77%; RR 1.1, 95% CI 1.01-1.2) and objective cure rates (92% vs 87%; RR 1.06, 95% CI 1.01-1.11). (Ogah et al, 2009).

In my experience, complications are largely user dependent and decrease with experience. For example, in my experience over the past 15 years, the risk of bladder injury has dropped from about 5% to less than 1%. The same is true for all complications. This is typical of many types of surgical procedures, and several studies have shown that surgeries performed by high volume surgeons have better outcomes. Others have reported that low volume surgeons had a 37% higher risk of

complications compared to high volume surgeons in a recent study published in JAMA Surgery, which analyzed data on 59,887 patients who received a synthetic sling for SUI (Welk et al, 2015).

V. Summary

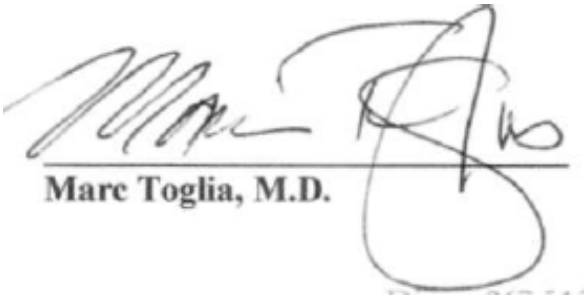
The use of TVT came as a necessity from the increasing rates of SUI in the population and the lengthy operating times, inpatient hospital stays, and recovery, and the significant morbidity, post-operative voiding dysfunction and long term failure rates with native tissue SUI repair like the Burch and autologous slings. These native tissue SUI repairs like the Burch and autologous slings are also complicated by dyspareunia and wound complications in a similar manner to what occurs with polypropylene MUS.

The original retropubic TVT sling stands alone in the field of surgical urogynecology as the most extensively studied anti-incontinence procedure in history. Over 2,000 scientific publications provide broad evidence supporting the use of polypropylene mid urethral slings as a treatment for SUI, with the majority of these publications concerning the TVT sling. The TVT has been studied in all types of patients, with and without medical co-morbidities, and across the entire spectrum of SUI disorders including primary and recurrent incontinence, mixed urinary incontinence, straightforward SUI with a hypermobile urethra as well as intrinsic sphincter deficiency. Multiple systematic reviews, meta-analyses and randomized, controlled trials have been published comparing the TVT to other established, non mesh SUI procedures, producing the highest level of scientific evidence supporting its clinical effectiveness and high level of patient satisfaction, as well as demonstrating superior safety and efficacy. No other surgical treatment for SUI before or since has been subject to such extensive investigation.

The issues of concern are not unique to TVT. They are a group of complications that are common to anti-incontinence procedures. Complications such as bleeding, hematoma, bladder and bowel injury occur with equal frequency in traditional procedures such as the Burch colposuspension and the autologous pubovaginal sling (Schimpf et al. 2014; AUA Revised SUI Guideline 2012; Novara et al, 2010). Similar problems have been seen with other procedures for SUI including the needle suspension procedures and fascial slings. These risks all decrease significantly as the user gains more experience. The rates of complications requiring surgery are consistently less than 5% across the TVT studies. Overall, the data from these high quality long term studies do not support the claims that

TVT places a women at a significant risk of long term, chronic complications or the need for reoperation as plaintiffs' experts suggest.

At the present time, expert opinion and clinical practice guidelines from a wide group of subspecialty societies, such as the American College of Obstetricians and Gynecologists, American Urogynecologic Society, Society of Gynecologic Surgeons, American Urological Association, Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction and the International Urogynecology Association advocate the polypropylene mid-urethral sling as the standard of care for the surgical treatment of SUI based on data derived from the TVT and acknowledge that it represents a great advance in the treatment of this condition in women. The TVT sling has revolutionized the treatment of SUI for women throughout the world and it has stood the test of time. Its design is useful, desirable and optimal and in my opinion it is reasonably safe for its untended use, to treat stress urinary incontinence. No other design or mesh has been demonstrated to be more effective, safer, or has been studied as much, as long, or in as many patients and types of patients as the TVT has showing that it is safe and effective. The TVT IFU, Surgeons Monograph and Professional Education are clear, useful and adequate to describe the procedure and potential risks. Risks of SUI surgery are obvious to surgeons and as surgeons, we are expected to be aware of the risks in light of our education, training and experience. Because of its utility and positive benefit / risk profile, the TVT has been adapted as the gold standard for its treatment.



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